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EP 0778266 A1 WO 98/50385 A1 WO 98/38177 A1
WO 98/18792 A1 WO 98/04560 A1 WO 96/25948 A1

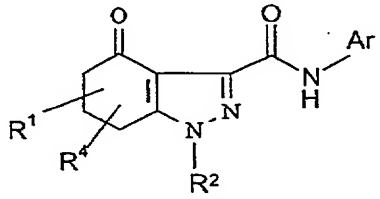
(58) Field of Search
Online: CAS ONLINE, EMBASE, EPODOC, JAPIO,
MEDLINE, WPI

(54) Abstract Title

Inverse agonist of GABA-A alpha-5 receptor subtype & amyloid ß production inhibitor combination & treating neurodegenerative conditions eg Alzheimer's disease

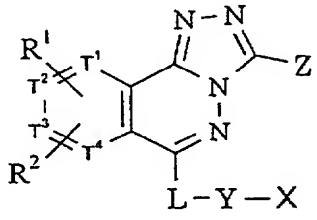
(57) There is disclosed a combination of an amyloid β production inhibitor and inverse agonist of the $GABA_A$ α5 receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease. These components act synergistically, thereby allowing for a lower overall dose of each to be administered, thus reducing side effects and decreasing any loss of effectiveness arising over a period of sustained use.

$GABA_A$ α5 inverse agonists include compounds of formula (I) or a pharmaceutically acceptable salt thereof (where the substituents are as defined in the specification):



(I)

and:



(I)

A particularly favoured compound for use in the present invention is 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methyloxy-1,2,4-triazolo[3,4-a]-phthalazine.

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A COMBINATION OF THERAPEUTIC AGENTS FOR TREATING ALZHEIMER'S DISEASE

The present invention relates to a combination of an amyloid β production inhibitor and inverse agonist of the $GABA_A$ α_5 receptor subtype, and the use of the combination in treating neurodegenerative conditions such as Alzheimer's Disease.

Alzheimer's Disease is a poorly understood neurodegenerative condition mainly affecting the elderly but also younger people who are generally genetically predispositioned to it.

The present invention provides a new and surprisingly effective synergistic combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α_5 receptor subtype.

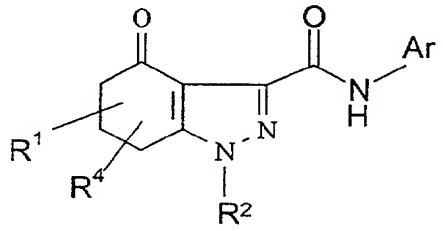
The present invention provides a greater than expected improvement in the condition of subjects suffering from a neurodegenerative disorder with an associated cognitive deficit, such as Alzheimer's Disease or Parkinson's disease, or from a cognitive deficit which may arise from a normal process such as aging or from an abnormal process such as injury, than would be expected from administration of the active ingredients alone. Further, the combination allows for a lower overall dose of each of the active ingredients to be administered thus reducing side effects and decreasing any reduction in the effectiveness of each of the active ingredients over time.

Any inverse agonist of the $GABA_A$ α_5 receptor subtype may be used which fulfills the criteria of WO-A-9625948. The inverse agonist may be either binding selective for the α_5 subtype or functionally selective, or both. Thus the inverse agonist is preferably an antagonist, or has insignificant agonist or inverse agonist properties at the other $GABA_A$ α receptor subtypes when measured in oocytes as described in WO-A-9625948. Specific

compounds are disclosed in WO-A-9804560, WO-A-9818792 and WO-A-9850385, WO-A-9962899 and WO-A-0012505.

A particularly favoured compound for use in the present invention is 3-(5-methylisoxazol-3-yl)-6-(1-methyl-1,2,3-triazol-4-yl)methyloxy-1,2,4-triazolo[3,4-a]-phthalazine.

A further class of $GABA_A$ α5 inverse agonists which can be used the present invention includes a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 and R^4 are independently chosen from hydrogen, halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{2-6} haloalkenyl and C_{2-6} haloalkynyl:

R^2 is hydrogen or C_{1-6} alkyl; and

Ar is phenyl, a 5-membered heterocyclic group containing 1, 2, 3 or 4 heteroatoms chosen from N, O and S, no more than one of which is O or S, or a 6-membered heterocyclic group containing one or two nitrogen atoms, each of which groups Ar is unsubstituted or substituted by from one to three groups independently chosen from halogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{2-6} alkenyloxy, C_{2-6} alkynyloxy, C_{3-7} cycloalkoxy, C_{1-6} haloalkyl, C_{2-6} haloalkenyl, C_{2-6} haloalkynyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, hydroxy, hydroxy C_{1-6} alkyl, cyano, nitro, amino C_{1-6} alkyl, C_{1-6} alkylaminoC_{1-6} alkyl or di(C_{1-6} alkyl)aminoalkyl.

R^1 is preferably hydrogen, halogen or C_{1-6} alkyl and is particularly hydrogen.

R^2 is preferably hydrogen or methyl especially hydrogen.

Ar is preferably phenyl or pyridine. When Ar is pyridine it may be 2-pyridine.

Ar is preferably unsubstituted or substituted with one or two groups independently selected from methyl, fluoro, chloro, methoxy, ethoxy, aminomethyl, aminoethyl or hydroxy, especially from methoxy, fluoro and aminoethyl.

Specific Examples of compounds of this class are:

4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid phenylamide;

4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid-2,5-difluorophenylamide;

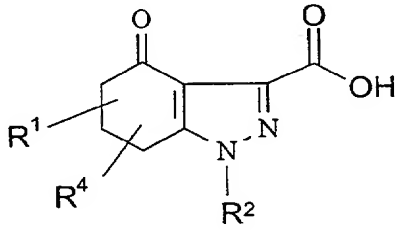
4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid pyridin-2-ylamide;

4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid 4-methoxyphenylamide; and

4-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid 4-(2-aminoethyl)phenylamide;

and the pharmaceutically acceptable salts thereof.

The compounds may be prepared byreacting a compound of formula II with a compound of formula III:



(II)

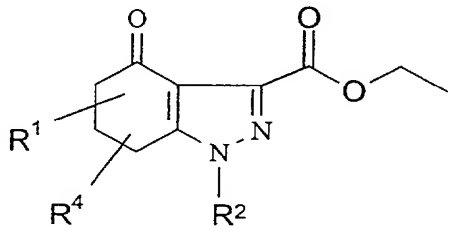
H_2N - Ar

(III)

wherein R^1, R^2, R^4 and Ar are as defined above. The reaction is generally carried out in a mixture of DMF/DCM and in the presence of a coupling agent such as 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride and dimethylaminopyridine. The reaction is generally carried out for about 36h.

If necessary any reactive portions of the moiety Ar are protected with a protecting group such as tert-butyloxycarbonyl. Such protecting groups can be removed after reaction of the compounds of formulae II and III to yield a compound of formula I.

The compound of formula II can be made by hydrolyzing a compound of formula IV:

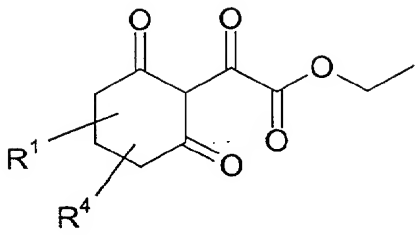


(IV)

wherein R^1, R^2 and R^4 are as defined above, with a base such as NaOH generally by heating at reflux for about 3h in a solvent such as EtOH.

The compound of formula IV wherein R^2 is other than hydrogen can be made by reaction of a compound of formula IV where R^2 is hydrogen with a strong base such as Na H followed by alkylation for example with the appropriate alkyl iodide.

The compound of formula IV is made by reacting a compound of formula V with a compound of formula VI:

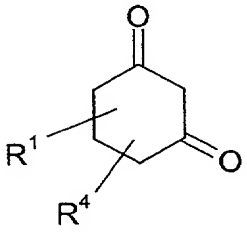


(V)

$H(R^2)NNH_2.HCl$

(VI)

The compound of formula V is made by reacting a compound of formula VII with a compound of formula VIII:



(VII)

ClC(O)C(O)OEt

(VIII)

wherein R^1 and R^4 are as defined above and the compound of formula VII is generally pre-reacted with trimethylsilylchloride.

wherein R^2 is as defined above, generally in a solvent such as DMF and in the presence of a base such at Et_3N at about 50°C for about 3 days.

Compounds of formulae III, V, VI, VII and VIII are commercially available or can be made from commercially available compounds by methods known in the art.

REFERENCE EXAMPLE 1

4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid phenylamide

Step 1: 4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester

A solution of 2-ethyloxalylcyclohexan-1,3-dione (6g, 28mmol) (Synthesis, 1976, 722) in DMF (30mL) was treated with hydrazine hydrochloride (1.9g, 28mmol) and triethylamine (3.9mL, 28mmol) and heated at 50°C for 3 days. After evaporating to dryness the residue was partitioned between water and DCM and the organic layer separated. The aqueous phase was re-extracted with DCM (x 2) and the combined organic layers dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel, using MeOH:DCM (2:98) as the eluent, to give an orange solid. The solid was trituated with ether to give the title compound (640mg, 11%) as a yellow solid. ^1H NMR (250MHz, d_6-DMSO) δ 1.28 (3H, t, J=7.1Hz), 2.00-2.10 (2H, m), 2.41 (2H, t, J=6.8Hz), 2.87 (2H, t, J=6.2Hz), 4.26 (2H, q, J=7.1Hz), 13.62 (1H, br s). MS, $(CI)^+$ 209 $(M+H)^+$. Found: C, 57.39; H, 5.76; N, 13.37%. $C_{10}H_{12}N_2O_3$ requires: C, 57.69; H, 5.81; N, 13.45%.

Step 2: 4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid

A solution of the foregoing ethyl ester (450mg, 2.2mmol) in EtOH (3mL) and NaOH (4N, 15mL) was heated at reflux for 3h. The cooled solution was acidified (conc. HCl), and the resultant solid isolated by filtration and washed with water. The solid was dried at 45°C in a vacuum oven to give the title compound (265mg, 67%) as a beige solid. ^1H NMR (360MHz, d_6-DMSO) δ 2.08-2.15 (2H, m), 2.60-2.64 (2H, m), 2.84-2.98 (2H, m), 14.03 (1H, br s). MS. $(CI)^+$ 181 $(M+H)^+$. Found: C, 52.33; H, 4.24; N, 15.00%. $C_8H_8N_2O_3.0.2H_2O$ requires: C, 52.29; H, 4.61; N, 15.24%.

Step 3: 4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid phenylamide

A suspension of the foregoing carboxylic acid (100mg, 0.55mmol) in DMF (2mL) and DCM (5mL) was treated with 1-(3-dimethylaminopropyl)-3-

ethyl carbodiimide hydrochloride (160mg, 0.83mmol), 4-dimethylaminopyridine (101mg, 0.83mmol) and aniline (77mg, 0.83mmol). The resultant solution was stirred for 36h then diluted with DCM (20mL) and washed with water (x1), 1N HCl (x2), sat. $NaHCO_3$ (x1) and water (x1). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel, eluting with DCM:MeOH (97:3) to give the title compound (90mg, 64%) as a colourless solid. mp 244°C (dec.). ^1H NMR (500MHz, d_6-DMSO) δ 2.09-2.14 (2H, m), 2.63-2.67 (2H, m), 2.80-2.95 (2H, m), 7.05-7.15 (1H, m) 7.30-7.40 (2H, m), 7.70-7.75 (2H, m) 12.24 (1H, br s), 13.68 and 14.20 (1H, 2 x br s) MS. $(CI)^+$ 256 $(M+H)^+$. Found: C, 64.22; H, 5.00; N, 15.97%. $C_{14}H_{13}N_3O_2.0.3H_2O$ requires: C, 64.51; H, 5.26; N, 16. 12%.

REFERENCE EXAMPLE 2

4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid-2,5-difluorophenylamide

The title compound was obtained using the procedure described in Example 1, Step 3 using 2,5-difluoroaniline. The amide (15mg, 19%) was isolated as a colourless solid. ^1H NMR (400 MHz, d_6-DMSO) δ 2.05-2.15 (2H, m), 2.60-2.68 (2H,m), 2.85-2.98 (2H, br s), 6.92-7.04 (1H, m), 7.30-7.40 (1H, m), 8.20-8.28 (1H, m), 12.43 (1H, br s), 13.83 and 14.35 (1H, 2 x br s). MS, $(CI)^+$ 292 $(M+H)^+$.

REFERENCE EXAMPLE 3

4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid pyridin-2-ylamide

The title compound was obtained using the procedure described in Example 1, Step 3 using 2-aminopyridine. The amide (33mg, 46%) was isolated as a cream solid. mp 250°C (dec.). ^{1}H NMR (400MHz, d_6-DMSO) δ 2.05-2.15 (2H, m), 2.62 (2H, t, J=6.2Hz), 2.85-2.95 (2H, br s). 7.10-7.20 (1H, m), 7.78-7.88 (1H, m), 8.24 (1H, d, J=8.3Hz), 8.35-8.41 (1H, m), 12.55 (1H, s), 13.78 and 14.26 (1H, 2 x br s). Found: C, 60.34; H, 4.34; N, 21.19%. $C_{13}H_{12}N_4O_2.0.05\ CH_2Cl_2$ requires: C, 60.17; H, 4.68; N, 21.51%. MS $(CI)^+$ 257 $(M+H)^+$.

REFERENCE EXAMPLE 4

4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid 4-methoxyphenylamide

The title compound was obtained using the procedure described in Example 1, Step 3 using *p*-anisidine. The amide (15mg, 19%) was isolated as a beige solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 2.07-2.13 (2H, m), 2.63 (2H, t, J=6.3Hz), 2.82-2.94 (2H, m), 3.76 (3H, s), 6.95 (2H, d, J=8.9Hz), 7.63 (2H, dd, J=6.8 and 2.1Hz), 12.14 (1H, br s), 13.65 and 14.20 (1H, 2 x br s). MS, $(CI)^+$: 286 $(M+H)^+$.

REFERENCE EXAMPLE 5

4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid 4-(2-aminoethyl)phenylamide

Step 1: 2-(4-Aminophenyl)ethyl carbamic acid *tert*-butyl ester

A solution of 2-(4-aminophenyl)ethylamine (1g, 7.3mmol) in DCM (20mL) at room temperature was treated with triethylamine (0.82g, 7.7mmol). After 10 min the solution was cooled to -5°C. Di-*tert*-butyldicarbonate (1.68g, 7.7mmol) was added portionwise over 10min and stirred for 30min before warming to room temperature. $NaHCO_3$ (sat. 2mL) was added followed by water (40mL). The organic layer was separated and aqueous re-extracted with DCM (x2). The combined organic layers were dried (K_2CO_3) and evaporated. The residue was purified by column chromatography on silica gel, eluting with EtOAc:hexane (1:4) to obtain the title compound (1.4g, 80%) as a yellow solid. ^1H NMR (360MHz, d_6-DMSO) δ 1.37 (9H, s), 2.49-2.51 (2H, m), 2.99-3.06 (2H, m), 4.83 (2H, s), 6.49 (2H, d, J=8.3Hz), 6.77-6.80 (1H, m), 6.81 (2H, d, J=8.3Hz) MS $(CI)^+$ 237 $(M+H)^+$.

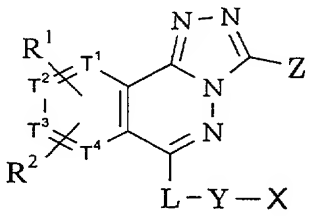
Step 2: [2-[4-(4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl)amino]phenyl]ethyl carbamic acid *tert*-butyl ester

The title compound was obtained using the procedure described in Example 1, Step 3 using the foregoing amine. The residue was purified by column chromatography on silica gel, eluting with DCM:MeOH (97:3) to give the amide (100mg, 45%) and was isolated as a colourless, low-melting solid. H NMR (400MHz, d_6-DMSO) 1.37 (9H, s), 2.07-2.14 (2H, m), 2.63 (2H, t, J=6.4Hz), 2.69 (2H, t, J=7.1Hz), 2.89 (2H, t, J=6.2Hz), 3.13-3.19 (2H, m), 6.52-6.65 (1H, m), 7.20 (2H, d, J=8.3Hz), 7.63 (2H, d, J=8.4Hz), 12.18 (1H, s), 14.00 (1H, br s).

Step 3: 4-Oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid 4-(2-aminoethyl)phenylamide

A suspension of the foregoing carbamate (100mg, 0.25mmol) in DCM (5mL) was treated with trifluoroacetic acid (0.5mL) and stirred at room temperature for 5h. The mixture was evaporated and residue partitioned between water and MeOH/DCM (5:95) and neutralised with $NaHCO_3$ (sat.). The organic layer was separated and the aqueous phase re-extracted with MeOH/DCM (5:95) (x2). The combined organic layers were dried (K_2CO_3) and evaporated. The residue was purified using column chromatography on silica gel, eluting MeOH:DCM (10:90) followed by DCM:MeOH:NH_3 (80:20:1). The title compound (35mg, 47%) was isolated as a cream solid. mp 250°C (dec.). ^{1}H NMR (360MHz, d_6-DMSO) δ 2.06-2.14 (2H, m), 2.63 (2H, t, J=6.7Hz), 2.68 (2H, t, J=6.9Hz), 2.84 (2H, t, J=7.6Hz), 2.89 (2H, t, J=6.4Hz), 7.24 (2H, d, J=8.4Hz), 7.67 (2H, d, J=8.5Hz), 12.39 (1H, s). MS, $(CI)^+$ 299 $(M+H)^+$.

A further class of $GABA_A$ α5 inverse agonists which can be used in the present invention includes a compound of the formula I:



(I)

wherein:

R^1 is hydrogen, halogen or CN or a group CF_3, OCF_3, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy or C_{2-4}alkynyloxy, each of which groups is unsubstituted or substituted with one or two halogen atoms or with a pyridyl or phenyl ring each of which rings may be unsubstituted or independently substituted by one or two halogen atoms or nitro, cyano, amino, methyl or CF_3 groups;

R^2 is hydrogen, halogen or CN or a group CF_3, OCF_3, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy or C_{2-4}alkynyloxy each of which groups is unsubstituted or substituted with one or two halogen atoms;

L is O, S or NR^n where R^n is H, C_{1-6}alkyl or C_{3-6}cycloalkyl;

one of T^1, T^2, T^3 and T^4 is nitrogen and the others are CH;

X is a 5-membered heteroaromatic ring containing 1, 2, 3 or 4 heteroatoms independently chosen from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur, or a 6-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms, the 5- or 6-membered heteroaromatic ring being optionally fused to a benzene ring and the heteroaromatic ring being optionally substituted by R^x and/or R^y and/or R^z, where R^x is halogen, R^3, OR^3, $OCOR^3$, NR^4R^5, NR^4COR^5, tri(C_{1-6}alkyl)silylC_{1-6}alkoxyC_{1-4}alkyl, CN or R^9, R^y is halogen, R^3, OR^3, $OCOR^3$, NR^4R^5, NR^4COR^5 or CN and R^z is R^3, OR^3 or $OCOR^3$, where R^3 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl and R^3 is optionally mono, di- or tri-fluorinated, R^4 and R^5 are each independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or CF_3 or R^4 and R^5, together with the nitrogen atom to which they are attached, form a 4-7 membered heteroaliphatic ring containing the nitrogen atom as the sole heteroatom, and R^9 is benzyl or an aromatic ring containing either 6 atoms, 1, 2 or 3 of which are optionally nitrogen, or 5 atoms, 1, 2 or 3 of which are independently chosen from oxygen, nitrogen and sulphur, at most one of the atoms being oxygen or sulphur, and R^9 is optionally substituted by one, two or three substituents independently chosen from halogen atoms and C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy and C_{2-4}alkynyloxy groups each of which groups is unsubstituted or substituted by one, two or three halogen atoms, and when X is a pyridine derivative, the pyridine derivative is optionally in the form of the N-oxide and providing that when X is a tetrazole derivative it is protected by a C_{1-4}alkyl group; or X is phenyl optionally

substituted by one, two or three groups independently selected from halogen, cyano, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl;

Y is optionally branched C_{1-4}alkylidene optionally substituted by an oxo group or Y is a group $(CH_2)_jO$ wherein the oxygen atom is nearest the group X and j is 2, 3 or 4;

Z is a 5-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur and providing that when one of the atoms is oxygen or sulphur then at least one nitrogen atom is present, or a 6-membered heteroaromatic ring containing 2 or 3 nitrogen atoms, Z being optionally substituted by R^v and/or R^w, where R^v is halogen, R^6, NR^7R^8, NR^7COR^8, CN, furyl, thienyl, phenyl, benzyl, pyridyl or a 5-membered heteroaromatic ring containing at least one nitrogen atom and optionally 1, 2 or 3 other heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the other heteroatoms being oxygen or sulphur and R^w is R^6 or CN;

R^6 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxyC_{1-6}alkyl, CH_2F or CF_3; and

R^7 and R^8 are each independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl or CF_3 or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 4-7 membered heteroaliphatic ring containing the nitrogen atom as the sole heteroatom;

or a pharmaceutically acceptable salt thereof.

The compound is generally in the form of the free base.

R^1 may be hydrogen, halogen or CN or a group C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy or C_{2-4}alkynyloxy, each of which groups is unsubstituted or substituted with one or two halogen atoms or with a pyridyl or phenyl ring each of which rings may be unsubstituted or

independently substituted by one or two halogen atoms or nitro, cyano, amino, methyl or CF_3 groups. R^1 is typically hydrogen, fluorine, chlorine, bromine or a group C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy or C_{2-4}alkynyloxy, each of which groups is unsubstituted or substituted with one or two halogen atoms or by a pyridyl or phenyl ring each of which rings may be unsubstituted or substituted by one or two halogen atoms or nitro, cyano, amino, methyl or CF_3 groups and is generally hydrogen, fluorine or pyridylmethoxy, typically hydrogen.

R^2 may be hydrogen, halogen or CN or a group C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, C_{2-4}alkenyloxy or C_{2-4}alkynyloxy each of which groups is unsubstituted or substituted with one or two halogen atoms. R^2 is typically hydrogen, fluorine, chlorine or bromine, and is generally hydrogen or fluorine, typically hydrogen.

Preferably L is an oxygen atom. L may also be NR^n in which R^n is preferably hydrogen or methyl. R^n may be hydrogen.

X is generally: pyridyl, pyrazinyl, pyridazinyl or pyrimidinyl optionally substituted by a halogen atom or a group R^3, OR^3, NR^4R^5 or a five membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms, and X is optionally fused to a benzene ring; a 5-membered heteroaromatic ring containing 2 or 3 heteroatoms chosen from oxygen, sulphur and nitrogen, at most one of the heteroatoms being oxygen or sulphur, which is unsubstituted or substituted by one, two or three groups independently chosen from halogen and R^3, or which is substituted by a pyridyl, phenyl or benzyl ring which ring is optionally independently substituted by one, two or three halogen atoms or C_{1-6}alkyl or CF_3 groups; or phenyl optionally substituted by one, two or three independently chosen halogen atoms. In particular X is pyridyl, pyrazinyl, pyridazinyl or pyrimidinyl which is unsubstituted or substituted by methyl, CF_3, methoxy, bromine, chlorine, isopropoxy, dimethylamino or a 5-membered heterocyclic ring containing 1, 2 or 3 nitrogen atoms, and X is

optionally fused to a benzene ring, or X is pyrazolyl, isothiazolyl, isoxazolyl, 1,2,4-triazolyl, thiazolyl, 1,2,3-triazolyl or imidazolyl which is unsubstituted or substituted by one, two or three groups independently chosen from methyl, CF_3 and chlorine or is substituted by a phenyl, benzyl or pyridyl ring which ring is unsubstituted or substituted by chlorine or CF_3, or X is phenyl which is unsubstituted or substituted by chlorine. Specific values of X are 2-pyridyl, 6-methylpyridin-2-yl, 3-pyridyl, 4-pyridyl, 3,5-dimethylpyrazol-1-yl, 3-methoxypyridin-2-yl, 3-methylisoxazol-5-yl, pyrazol-1-yl, 6-chloropyridin-2-yl, 6-bromopyridin-2-yl, 6-methoxypyridin-2-yl, 6-isopropoxypyridin-2-yl, 6-*N,N*-dimethylpyridin-2-yl, 6-(imidazol-1-yl)pyridin-2-yl, 3-pyridazino, 4-pyrimidinyl, pyrazin-2-yl, 2-quinolinyl, 2-quinoxalyl, 2-(4-trifluoromethyl)pyridyloxy, 4-methylisothiazolyl, 2,6-dichlorophenyl, 4-methylthiazol-5-yl, 2-methylthiazol-4-yl, 2-[1-(3-trifluoromethyl)pyrid-6-yl]imidazolyl, 1-benzylimidazol-2-yl, 1-(4-chlorophenyl)-1,2,3-triazol-4-yl, 3-chloro-2-methyl-5-trifluoromethylpyrazol-4-yl, 1-methyl-1,2,4-triazol-3-yl, (5-trifluoromethyl)pyridyl-2-yl, (3-trifluoromethyl)pyrid-2-yl, (4-trifluoromethyl)pyrid-2-yl, 1-methylimidazol-2-yl, 2-{[2-(trimethylsilyl)ethoxy]methyl}-1,2,4-triazol-3-yl, 3-methylimidazol-4-yl, 1,2,4-triazol-3-yl, 1-isopropyl-1,2,4-triazol-3-yl, 4-methyl-1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, isothiazol-3-yl, 1-ethyl-1,2,4-triazol-3-yl, 2-methyl-1,2,3-triazol-4-yl, 1-methyl-1,2,3-triazol-4-yl, 2-methyl-1,2,4-triazol-3-yl, 1-methylimidazol-4-yl, 5-tert-butylpyridazin-3-yl and 1-methyl-1,2,3-triazol-5-yl. Still further particular values of X are 2-benzyl-1,2,4-triazol-3-yl, 1-benzyl-1,2,4-triazol-3-yl, 1-*n*butyl-1,2,4-triazol-3-yl, 2-ethyl-1,2,4-triazol-3-yl, 2-methylpyrazol-3-yl, 1-methylpyrazol-3-yl, 1-*n*propyl-1,2,4-triazol-3-yl, 1-(2,2,2-trifluorethyl)-1,2,4-triazol-3-yl, 1-ethyl-1,2,3-triazol-5-yl, 1-methyltetrazol-2-yl, imidazol-2-yl, 2-*n*propyl-1,2,4-triazol-3-yl, 1-ethyl-1,2,3-triazol-4-yl, 2-ethyl-1,2,3-triazol-4-yl, 1-ethylimidazol-5-yl, 1-ethylimidazol-4-yl, 1-*n*propyl-1,2,4-triazol-3-yl and 1-ethyl-1,2,3-triazol-5-yl. In particular X is pyrid-2-yl, 2-methyl-1,2,4-triazol-3-

yl, 1-methyl-1,2,4-triazol-3-yl, 1-methyl-1,2,3-triazol-4-yl, 3-methyl-1,2,3-triazol-4-yl or 2-ethyl-1,2,4-triazol-3-yl.

When X is a substituted 6-membered heteroaromatic ring:
R^x is preferably halogen, R^3, OR^3, NR^4R^5 or a five-membered heteroaromatic ring containing 1, 2 or 3 nitrogen atoms and more preferably methyl, CF_3, methoxy, bromine, chlorine, isopropoxy, dimethylamino or a five-membered heterocyclic ring containing 1, 2 or 3 nitrogen atoms; and R^y and R^z are preferably absent. In particular X is optionally substituted pyridine. The optional substituents are generally halogen or C_{1-6}alkyl, particularly methyl or ethyl, especially methyl. When X is pyridine it may be in the form of the N-oxide.

When X is a substituted 5-membered heteroaromatic ring:
R^x is preferably halogen, R^3 or a pyridyl, phenyl or benzyl ring which ring is optionally independently substituted by one, two or three halogen atoms or C_{1-6}alkyl or CF_3 groups and more preferably R^x is methyl, CF_3, chlorine or a phenyl, pyridyl or benzyl ring which ring is unsubstituted or substituted by chlorine or CF_3; and R^y and R^z are preferably halogen or R^3, and more preferably methyl, CF_3 or chlorine. X is especially an optionally substituted triazole, either a 1,2,3- or 1,2,4-triazole, which is preferably substituted by methyl or ethyl, especially methyl.

Particularly aptly X is an unsubstituted six-membered heteroaromatic group containing one or two nitrogen atoms.

Apt values for Y include CH_2, $CH(CH_3)$, CH_2CH_2 and $CH_2CH_2CH_2$ optionally substituted by an oxo group, and CH_2CH_2O and $CH_2CH_2CH_2O$. For example, Y can be CH_2, CH_2CH_2, $CH_2CH_2CH_2$, CH_2CH_2O or $CH_2CH_2CH_2O$. Preferably Y is CH_2 or CH_2CH_2 and most preferably CH_2.

R^v is suitably chlorine, R^6, thienyl, furyl, pyridyl or NR^7R^8, more particularly R^6, thienyl, furyl, pyridyl or NR^7R^8, for example C_{1-6}alkyl, C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, pyridyl, thienyl or amino and more

particularly methyl, ethyl, ethoxy, isopropyl, cyclopropyl, thienyl or pyridyl, and even more particularly methyl, ethyl, isopropyl, cyclopropyl, thienyl or pyridyl. A further example of R^v is chlorine.

R^w is suitably R^6, for example C_{1-6}alkyl, CH_2F or hydroxyC_{1-6}alkyl, more particularly methyl, CH_2F or hydroxymethyl. Generally R^w is absent.

R^x may be halogen, R^3, OR^3, $OCOR^3$, NR^4R^5, NR^4COR^5, CN or R^9.

Z is preferably a 5-membered heteroaromatic ring containing 1, 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the heteroatoms being oxygen or sulphur and providing that when two of the heteroatoms are nitrogen an oxygen or sulphur atom is also present and that when one of the atoms is oxygen or sulphur then at least one nitrogen atom is present, or a 6-membered heteroaromatic ring containing 2 or 3 nitrogen atoms, Z being optionally substituted by R^v and/or R^w, where R^v is halogen, R^6, NR^7R^8, NR^7COR^8, CN, furyl, thienyl, phenyl, benzyl, pyridyl or a 5-membered heteroaromatic ring containing at least one nitrogen atom and optionally 1, 2 or 3 other heteroatoms independently selected from oxygen, nitrogen and sulphur, at most one of the other heteroatoms being oxygen or sulphur and R^w is R^6 or CN.

Suitable values for Z include pyrimidinyl, pyrazinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl and thiadiazolyl groups which groups are optionally substituted by R^6 , thienyl, furyl, pyridyl or NR^7R^8 groups.

Z is very aptly a 5-membered heteroaromatic ring containing one oxygen and one or two nitrogen ring atoms and is optionally substituted by a group R^6. In such compounds R^6 is favourably a methyl group.

Favoured values for Z include optionally substituted isoxazoles and oxadiazoles.

Z may be unsubstituted.

Z may very aptly be substituted by methyl.

Z is especially isoxazole which is unsubstituted or substituted by C_{1-6}alkyl or C_{1-6}alkoxy, especially methyl or ethoxy.

Particular values of Z are 3-methyloxadiazol-5-yl, 3-cyclopropyloxadiazol-5-yl, 5-methylisoxazol-3-yl, 5-(3-pyridyl)-isoxazol-3-yl, 5-hydroxymethylisoxazol-3-yl, 4,5-dimethylisoxazol-3-yl, 5-ethylisoxazol-3-yl, 5-cyclopropylisoxazol-3-yl, 5-isopropylisoxazol-3-yl, isoxazol-3-yl, 5-thienylisoxazol-3-yl, 5-fluoromethylisoxazol-3-yl, 4-methylisoxazol-3-yl, 5-ethoxyisoxazol-3-yl, 4-methyl-5-chloroisoxazol-3-yl, 5-trifluoromethylisoxazol-3-yl, 5-(pyrid-2-yl)isoxazol-3-yl, 5-benzylisoxazol-3-yl, 5-chloroisoxazol-3-yl, 3-cyclopropyloxadiazol-5-yl, 5-methoxyisoxazol-3-yl, 5-methoxymethylisoxazol-3-yl, 5-methyloxadiazol-3-yl, pyrazin-2-yl and 3-methylisoxazol-5-yl. In particular Z is 5-methylisoxazol-3-yl, isoxazol-3-yl or 5-ethoxyisoxazol-3-yl.

R^3 may be C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl or CF_3.

Generally R^3 is C_{1-6}alkyl, C_{1-6}alkoxy or CF_3. In particular R^3 is methyl, methoxy, ispropoxy or trifluoromethyl.

Generally R^4 and R^5 are independently hydrogen or C_{1-6}alkyl, in particular hydrogen or methyl, for example both can be methyl.

R^6 may be C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, CH_2F or CF_3. Generally R^6 is CH_2F, CF_3, C_{1-6}alkoxy, C_{3-6}cycloalkoxy, C_{1-6}alkyl or hydroxyC_{1-6}alkyl, for example, CH_2F, CF_3, methyl, ethyl, isopropyl, cyclopropyl or hydroxymethyl, particularly methyl or cyclopropyl. Alternatively R^6 is C_{1-6}alkyl or hydroxyC_{1-6}alkyl, for example, methyl, ethyl, isipropyl, cyclopropyl or hydroxymethyl.

Generally R^7 and R^8 are independently hydrogen or C_{1-6}alkyl, particularly hydrogen or methyl.

Generally R^9 is pyrazolyl, imidazolyl, phenyl, benzyl or pyridyl optionally substituted by halogen, preferably chlorine, or CF_3. In particular

R^9 can be imidazol-1-yl, 3-trifluoromethylpyrid-5-yl, benzyl and 4-chlorophenyl.

Generally R^{10} is C_{1-6}alkyl or CF_3, in particular methyl or CF_3, for example CF_3.

In a preferred subclass of compounds of formula I:

R^1 and R^2 are hydrogen;

L is O;

X is pyridine or triazole and is unsubstituted or substituted by C_{1-6}alkyl;

Y is CH_2; and

Z is isoxazole which is unsubstituted or substituted by C_{1-6}alkyl or C_{1-6}alkoxy.

Specific compounds within this class include:

3-(5-methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta [a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,9-pentaaza-cyclopenta [a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,7-pentaaza-cyclopenta [a]napthalene;

3-(5-methylisoxazol-3-yl)-5(2-pyridylmethyloxy)-1,2,3a,4,8-pentaaza-cyclopenta[a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(2-methyl-1,2,4-triazol-3-ylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-ethoxyisoxazol-3-yl)-5-(1-methyl-1,2,4-triazol-3-ylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-isoxazol-3-yl-5-(2-methyl-1,2,4-triazol-3-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-isoxazol-3-yl-5-(1-methyl-1,2,4-triazol-3-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(1-methyl-1,2,4-triazol-3-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(1-methyl-1,2,3-triazol-4-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-methylisoxazol-3-yl)-5-(3-methyl-1,2,3-triazol-4-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-methylisolxazol-3-yl)-5-(2-ethyl-1,2,4-triazol-3-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

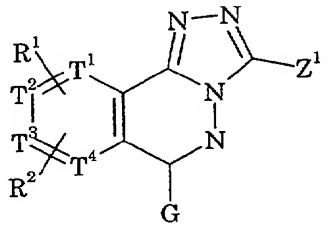
3-(5-ethoxyisoxazol-3-yl)-5-(1-methyl-1,2,3-triazol-4-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

3-(5-ethoxyisoxazol-3-yl)-5-(3-methyl-1,2,3-triazol-4-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

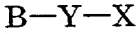
3-(5-ethoxyisoxazol-3-yl)-5-(2-ethyltriazol-1,2,4-3-ylmethoxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene;

and pharmaceutically acceptable salts thereof.

The compounds of this class may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:



(III)

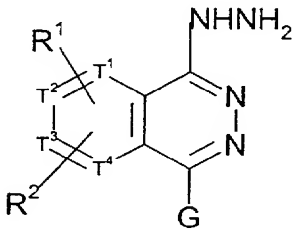


(IV)

wherein T^1, T^2, T^3, T^4, R^1, R^2, X and Y are as defined above, G is a leaving group such as chlorine, OCH_2CF_3 or tosylate, B is LH where L is as defined above and Z^1 is a group Z as defined above or is a moiety which can be converted into a group Z by further reaction.

The reaction between compounds III and IV when L is O is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride or lithium bis(trimethylsilyl)amide, typically without heating and under an inert atmosphere such as nitrogen. When L is NR^n the reaction is conveniently effected in the presence of a strong base such as Et_3N or NaH and a solvent such as DMF or DMSO generally for 15 to 60 hours with heating to 50-120°C.

The intermediates of formula III above may be prepared by reacting a compound of formula V, which constitutes a further feature of the present invention, with a compound of formula VI:



(v)

(vi)

wherein T^1, T^2, T^3, T^4, R^1, R^2, G and Z^1 are as defined above, and W represents a suitable leaving group such as C_{1-6}alkoxy, chlorine or hydroxy.

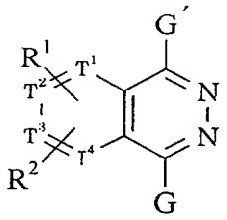
The reaction is advantageously conducted in an inert organic solvent, generally in the presence of an organic nitrogen base and preferably under an inert atmosphere such as nitrogen. Suitable solvents include xylene, dioxane, tetrahydrofuran and lower aliphatic halogenated and aromatic hydrocarbons. Suitable organic nitrogen bases that may be employed include trialkylamines and pyridine. The reaction is generally conducted at a temperature range of

from -20°C to the reflux temperature of the reaction mixture, for a period of time that depends on the reactants employed and the temperature at which the reaction is carried out. The compound of formula VI may be activated by reacting with a compound such as bis (2-oxo-3-oxazolidinyl)phosphinic chloride or 1,1′-dicarbonyldiimidazole before reaction with the hydrazine.

When Z^1 is not a group Z, it is, for example, an allylformyloxime group which can be converted to a carboxaldehydeoxime using tetrakis(triphenylphosphine)palladium(0) generally under an inert atmosphere such as nitrogen in the presence of triethylammonium formate, in a solvent such as ethanol for about 18 hours. The carboxaldehydeoxime can be converted to a carboxaldehydechloroxime by reacting with a chlorinating agent such as N-chlorosuccinimide in a solvent such as DMF. The carboxaldehydechloroxime can be converted to the desired group Z by reacting with an unsaturated compound such a vinylidene chloride, methyl propargyl ether, 3-phenyl-1-propyne, 2-pyridylacetylene, trifluoromethylacetylene or ethoxyacetylene generally in the presence of a base such a triethylamine, and a solvent such as dichloromethane. Alternatively, the carboxaldehydechloroxime can be converted to a group Z by reacting with ammonium hydroxide generally in a solvent such as ethanol for about 30 minutes and then acetic anhydride generally with heating to reflux for about 16 hours.

Compounds of formula III in which G is OCH_2CF_3 can be prepared by reacting a compound of formula III in which G is chlorine with 2,2,2-trifluoroethanol in the presence of a base such as lithium bis(trimethylsilyl)amide generally in a solvent such as DMF, preferably with cooling to about -20°C-0°C for a period of about 30 minutes.

The compound of formula V is prepared by reaction of a compound of formula VII:



(VII)

where T^1, T^2, T^3, T^4, R^1, R^2 and G are as defined above, and G′ is another suitable leaving group which may be the same as or different to G, with hydrazine, usually in the form of its monohydrate, generally in a solvent such as ethanol and generally by refluxing for a suitable period such as 15 minutes to 2 hours.

As the compound of formula VII is asymmetrical, the substitution pattern about the fused benzene ring is not symmetrical. Consequently the reaction between this compound and hydrazine will usually give rise to a mixture of isomeric products depending on whether group G or G′ is displaced first. Thus in addition to the required product of formula V, the isomeric compound wherein the R^1 and R^2 moieties are reversed or where the nitrogen atom in the fused pyridine ring is in its alternative location, will usually be obtained to some extent. For this reason it will generally be necessary to separate the resulting mixture of isomers by conventional methods such as chromatography.

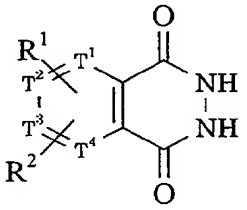
The compound of formula VII can be used to prepare a compound of formula III in a single step by reacting with the appropriate hydrazoic acid, that is a compound of formula XIII:

$H_2NNHC(O)Z$

(XIII)

wherein Z is as defined above. This is generally carried out in the presence of a base, such as triethylamine, in a solvent such as xylene, at reflux under an inert atmosphere such as nitrogen.

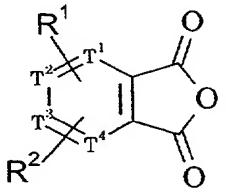
The compound of formula VII can be prepared by reacting a compound of formula X:



(X)

where T^1, T^2, T^3, T^4, R^1 and R^2 are as defined above, with a suitable reagent for introducing leaving groups G and G^1, for example where G and G^1 are both chlorine $POCl_3$ can be used generally with heating to reflux for about 16 hours.

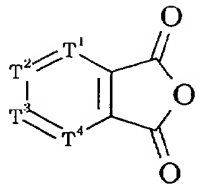
The compound of formula X can be prepared by reacting a compound of formula XI with hydrazine hydrate ($H_2NNH_2.H_2O$):



(XI)

where T^1, T^2, T^3, T^4, R^1 and R^2 are as defined above. The reaction is generally carried out in a protic solvent, such as 40% aqueous acetic acid, and in the presence of a buffering agent such as sodium acetate, generally with heating to reflux for about 16 hours to about 4 days.

The compound of formula XI can be prepared by reaction of a compound of formula XII:

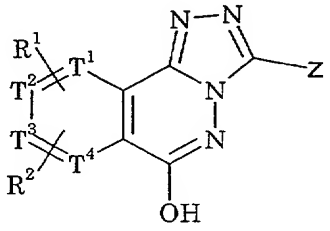


(XII)

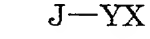
wherein T^1, T^2, T^3 and T^4 are as defined above with suitable reagents to introduce the substituents R^1 and R^2 where necessary. For example, when R^1 is phenyloxy or pyridyloxy or a derivative thereof, the corresponding hydroxy compound can be used as a reagent. The compounds of formula XII are commercially available.

Alternatively, when R^1 is the same as L-Y-X in the compound of formula I, it can be introduced by displacing another group R^1 which can act as a leaving group, such as fluorine, in the reaction between the compounds of formulae III and IV.

In another procedure, the compounds of this class wherein L is O may be prepared by a process which comprises reacting a compound of formula VIII with a compound of formula IX:



(VIII)



(IX)

wherein T^1, T^2, T^3, T^4, R^1, R^2, X, Y and Z are as defined above and J represents a suitable leaving group such as a halogen atom, typically

chlorine. The reaction between compounds VIII and IX is conveniently effected by stirring the reactants in a suitable solvent, typically *N,N*-dimethylformamide, in the presence of a strong base such as sodium hydride.

The intermediates of formula VIII above may be conveniently prepared by reacting a compound of formula III as defined above with an alkaline hydroxide, e.g. sodium hydroxide. The reaction is conveniently effected in an inert solvent such as 1,4-dioxane, ideally at the reflux temperature of the solvent. A compound of formula III in which G is para-sulphonyltoluene can be made by reacting a compound of formula VIII with 4-toluenesulphonylchloride.

Where they are not commercially available, the starting materials of formula IV, VI, VIII and IX may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods known from the art.

It will be understood that any compound of formula I initially obtained from the above process may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art.

REFERENCE EXAMPLE 6

3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta [a]naphthalene

a) 6,7-Dihydro-pyrido[2,3-d]pyridazine-5,8-dione

Hydrazine hydrate (13.09g, 0.261mol) was added to a stirred solution of pyridine-2,3-dicarboxylic anhydride (30.0g, 0.201mol) and sodium acetate (21.45g, 0.261mol) in 40% acetic acid/water (400ml). The

reaction was heated at reflux for 3 days under nitrogen. The yellow precipitate was filtered off and washed successively with water (4 x 200ml), hexane (3 x 150ml) and diethyl ether (3 x 150ml) to give the title-compound (25.0g, 76%), ^{1}H NMR (250MHz, d^6-DMSO) δ 7.90 (1H,q, J=4.5Hz, Ar-H), 8.51 (1H, d, J=4.5Hz, Ar-H), 9.13 (1H, d, J=4.6Hz, Ar-H), 11.65 (2H, br s, 2 of NH); MS (ES$^+$) m/e 164 $[MH]^+$.

b) 5,8-Dichloro-pyrido[2,3-d]pyridazine

The preceding compound (25.0g, 0.185mol) was dissolved in phosphorus oxychloride (260ml) and heated at reflux for 4h under nitrogen. The solvent was removed in vacuo and the resulting brown solid was taken up in dichloromethane (300ml) and water (100ml) and sodium hydrogen carbonate added until the mixture was neutral. The mixture was filtered and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 200ml) and the combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The brick-red coloured solid was dissolved in hot dichloromethane, filtered and triturated with diethyl ether to give the title-compound (15.2g, 50%), ^{1}H NMR (250MHz, $CDCl_3$) δ 7.25 (1H, m, Ar-H), 7.87 (1H, q, J=4.6Hz, Ar-H), 8.03 (1H, d, J=4.6Hz, Ar-H).

c) 5-Methylisoxazole-3-carboxylic acid hydrazide

To a solution of ethyl 5-methylisoxazole-3-carboxylate (3.0g, 19mmol) in methanol (30ml) at 0°C under nitrogen was added hydrazine hydrate (3.04g, 95mmol) over 0.3h. The reaction was stirred at 0°C for 0.25h and at RT for 1h. The white precipitate was filtered off and washed with methanol to give the title-compound (0.78g, 29%) as a

white solid, ^{1}H NMR (250MHz, $CDCl_3$) δ 2.41 (3H, d, J=0.8 Hz,CH_3), 4.07 (2H, br s, NH_2), 6.44 (1H, q, J=0.8 Hz, Ar-H), 7.99 (1H, br s, N-H); MS (ES^+) m/e 142 $[MH]^+$.

d) 5-Chloro-3-(5-methylisoxazol-3-yl)-1,2,3a,4,6-pentaaza-cyclopenta[a] naphthalene and 5-Chloro-3-(5-methyl-isoxazol-3-yl)-1,2,3a,4,9-pentaaza-cyclopenta[a]naphthalene

To a solution of 5,8-dichloro-pyrido[2,3-d]pyridazine (2.21g, 11mmol) and 5-methylisoxazole-3-carboxylic acid hydrazide (1.57g, 11mmol) in xylene (70ml) was added triethylamine (1.55ml, 11mmol). The reaction was heated at reflux under nitrogen for 16h. The solvent was evaporated in vacuo and the residue taken up in dichloromethane (150ml), washed with water (3 x 75ml), dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by chromatography on silica gel, eluting with 4% methanol/dichloromethane. The two isomers were separated by chromatography on alumina (Grade III), eluting with 0.5% ethanol/dichloromethane to give:

5-chloro-3-(5-methylisoxazol-3-yl)-1,2,3a,4,9-pentaaza-cyclopenta[a] naphthalene (more polar isomer)(0.25g, 8%): ^{1}H NMR (360MHz, d^6-DMSO) δ 3.31 (3H, s, CH_3), 7.01 (1H, d, J=0.8 Hz, Ar-H), 8.08 (1H, q, J=4.5Hz, Ar-H), 8.75 (1H, d, J=4.5Hz, Ar-H) 9.33 (1H, q, J= 4.7Hz, Ar-H).

5-chloro-3-(5-methylisoxazol-3-yl)-1,2,3a,4,6-pentaaza-cyclopenta[a] naphthalene (less polar isomer) (0.4g, 13%): ^{1}H NMR (360MHz, d^6-DMSO) δ 3.31 (3H, s, CH_3), 7.01 (1H, d, J=0.7Hz, Ar-H), 8.15 (1H, q, J=4.6Hz, Ar-H), 9.04 (1H, dd, J=8.2Hz and 1.6Hz, Ar-H), 9.27 (1H, dd, J= 4.6Hz and 1.5Hz, Ar-H).

e) 3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta [a]naphthalene

Sodium hydride (63mg of a 60% dispersion in oil, 1.57mmol) was added to a stirred solution of 2-pyridyl carbinol (87mg, 0.84mmol) in DMF (15ml) at room temperature under nitrogen and the mixture stirred for 0.25h. After this time the less polar chloride (225mg, 0.79mmol) was added and the mixture stirred for 2h. The solvent was evaporated in vacuo and the residue dissolved in dichloromethane, washed with water (x2), dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography of the residue on silica gel, eluting with 4% methanol/dichloromethane, gave the title-product (100mg, 35%), ^1H NMR (360MHz, $CDCl_3$) δ 2.59 (3H, d, J=0.7Hz, CH_3), 5.88 (2H, s, CH_2), 6.81 (1H, s, Ar-H), 7.27 (1H, m, Ar-H), 7.71-7.77 (2H, m, 2 of Ar-H), 7.89 (1H, q, J=4.7Hz, Ar-H), 8.70 (1H, d, J=4.7Hz, Ar-H), 9.00 (1H, q, J=8.1Hz, Ar-H), 9.18 (1H, q, J=4.5Hz, Ar-H); MS (ES^+) m/e 360 $[MH]^+$; Anal. Found. C, 59.36; H, 3.36; N, 26.80. $C_{18}H_{13}N_7O_2$. 0.1 (CH_2Cl_2) requires C, 59.10; H, 3.61; N, 26.65%.

REFERENCE EXAMPLE 7

3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,9-pentaaza-cyclopenta [a]naphthalene

The title-compound was prepared from 5-chloro-3-(5-methylisoxazol-3-yl)-1,2,3a,4,9-pentaaza-cyclopenta[a]naphthalene according to the procedure given in Example 6, part e.

^1H NMR (360MHz, $CDCl_3$) δ 2.59 (3H, s, Ar-H), 5.78 (2H, s, CH_2), 6.85 (1H, d, J=0.8Hz, Ar-H), 7.29 (1H, m, Ar-H), 7.74-7.79 (3H, m, 3 of Ar-H), 8.62 (1H, d, J=8.0Hz, Ar-H), 8.70 (1H, d, J=4.6Hz, Ar-H), 9.23

(1H, q, J=4.6Hz, Ar-H); MS (ES^+) m/e 360 $[MH]^+$. Anal. Found. C, 60.02; H, 3.31; N, 27.00. $C_{18}H_{13}N_7O_2$ requires C, 60.16; H, 3.65; N, 27.28%.

REFERENCE EXAMPLE 8

3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,7-pentaaza-cyclopenta[a]naphthalene and 3-(5-Methylisoxazol-3-yl)-5(2-pyridylmethyloxy)-1,2,3a,4,8-pentaaza-cyclopenta[a]naphthalene

The title-compounds were prepared as described in Example 6, parts a-e, using pyridine-3,4 dicarboxylic anhydride instead of pyridine-2,3-dicarboxylic anhydride in part a. The isomers were separated in part e by HPLC:

3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,7-pentaaza-cyclopenta [a]naphthalene: ^1H NMR (500MHz, $CDCl_3$) δ 2.73 (3H, s, CH_3), 5.94 (2H, s, CH_2), 6.97 (1H, s, Ar-H), 7.47 (1H, t, J=6.0Hz, Ar-H), 7.90-7.96 (2H, m, 2 of Ar-H), 8.62 (1H, d, J=5.3Hz, Ar-H), 8.82 (1H, d, J=4.6Hz, Ar-H), 9.27 (1H, d, J=5.3Hz, Ar-H), 9.75 (1H, s, Ar-H); MS (ES^+) m/e 360 $[MH]^+$.

3-(5-Methylisoxazol-3-yl)-5-(2-pyridylmethyloxy)-1,2,3a,4,8-pentaaza-cyclopenta [a]naphthalene: ^1H NMR (360MHz, $CDCl_3$) δ 2.60 (3H, d, J=0.7Hz, CH_3), 5.78 (2H, s, CH_2), 6.82 (1H, s, Ar-H), 7.31 (1H, m, 2 of Ar-H), 7.74-7.78 (2H, m, 2 of Ar-H), 8.08 (1H, d, J=4.5Hz, Ar-H), 8.70 (1H, d, J=4.5Hz, Ar-H), 9.08 (1H, d, J=5.3Hz), 10.03 (1H, s, Ar-H); MS (ES^+) m/e 360 $[MH]^+$.

REFERENCE EXAMPLE 9

3-(5-Methylisoxazol-3-yl)-5-(2-methyl-1,2,4-triazol-3-ylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

A solution of 5-chloro-3-(5-methylisoxazol-3-yl)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene (100mg, 0.35mmol) in N,N-dimethyl formamide (7ml) was added to a solution of 2-methyl-1,2,4-triazole-3-methanol (43mg, 0.38mmol) (prepared using the conditions of Itoh and Okongi, EP-A-421210) under nitrogen, and the mixture cooled to -78°C. Lithium bis(trimethylsilyl)amide (0.42ml, 1.0M in tetrahydrofuran, 0.42mmol) was added, and the reaction stirred at -78°C for 2h, then allowed to warm to room temperature and stirred for 3h. The solvents were evaporated by azeotroping with xylene and the residue pre-absorbed onto silica (1g) from methanol/dichloromethane. Flash chromatography on a silica bond elute cartridge (10g) eluting with a 0% → 5% methanol/dichloromethane gradient, followed by recrystallisation (dichloromethane/ethyl acetate) gave the title-product (52mg, 41%), mp 255-257°C; ^{1}H NMR (360MHz, $CDCl_3$) δ 9.16 (1H, dd, J=4.4Hz and 1.7Hz, Ar-H), 9.01 (1H, dd, J=8.2Hz and 1.7Hz, Ar-H), 7.92 (1H, m, Ar-H), 7.90 (1H, s, Ar-H), 6.93 (1H, s, Ar-H), 5.88 (2H, s, CH_2), 4.12 (3H, s, CH_3), 2.60 (3H, s, CH_3); MS (ES^+) m/e 364 $[MH]^+$.

REFERENCE EXAMPLE 10

3-(5-Ethoxyisoxazol-3-yl)-5-(1-methyl-1,2,4-triazol-3-ylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

a) 4-Chloro-1-hydrazino-2,3,5-azanaphthalene and 1-chloro-4-hydrazino-2,3,5-azanaphthalene

To a solution of 5,8-dichloropyrido[2,3-d]pyridazine (21.5g, 108mmol) (prepared as described in example 6, part b) in ethanol (600ml) was added hydrazine hydrate (32.4g, 65mmol). The reaction was stirred at room temperature for 18h and the precipitate filtered off and washed with diethyl ether to give the title compounds as a brick red solid (21.0g, 100%), ^{1}H NMR (250MHz, d^6-DMSO) δ 9.16 (1H, m, Ar-H), 8.45 (1H, m, Ar-H), 8.03 (1H, m, Ar-H), 4.69 (2H, br s, NH_2). The regioisomers were separated by chromatography.

b) 5-Chloro-3-dichloromethyl-1,2,3a,4,6-pentaaza-cyclopenta[a] naphthalene

To the preceding hydrazine (54g, 277mmol) in toluene (400ml) was added dichloroacetic acid (150ml) and the reagents heated under Dean-Stark conditions for 1.5h. On cooling, saturated potassium carbonate solution (aq) (200ml) was added. The emulsion formed was filtered through celite, and the filtrate evaporated in vacuo. The residue was taken in dichloromethane and washed with water (x2). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The required isomer was separated by chromatography on silica gel, eluting with 20% → 100% ethyl acetate/hexane to give the title-compound (4.69g, 6%) (less polar isomer), ^{1}H NMR (250MHz, $CDCl_3$) δ 7.32 (1H, s, C-H), 7.99 (1H, m, Ar-H), 9.05 (1H, dd, J=1.6Hz and 8.1Hz, Ar-H) 9.26 (1H, dd, J=1.7Hz and 4.6Hz, Ar-H).

c) 3-Dichloromethyl-5-(2,2,2-trifluoroethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

A solution of the preceding chloride (4.69g, 16mmol) in N,N-dimethylformamide (40ml) was added to a solution of 2,2,2-trifluoroethanol (1.3ml, 17.8mmol) in tetrahydrofuran (30ml), under nitrogen, and the mixture cooled to -78°C. Lithium bis(trimethylsilyl)amide (19.5ml, 1.0M in tetrahydrofuran, 19.5mmol) was added, and the mixture stirred at -78°C for 0.5h, then at room temperature for 2h. The solvent was evaporated in vacuo by azeotroping with xylene, and the residue partitioned between dichloromethane and water. The aqueous phase was separated and extracted with dichloromethane (x3). The combined organic phases were dried ($MgSO_4$) and the solvent in vacuo. Flash chromatography of the residue on silica gel, eluting with 1% → 3% methanol/ dichloromethane gave the title-compound (2.5g, 44%), ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.24 (1H, dd, J=4.6Hz and 1.6Hz, Ar-H), 8.99 (1H, dd, J=8.2Hz and 1.7Hz, Ar-H) 7.95 (1H, m, Ar-H), 7.28 (1H, s, C-H) 5.08 (2H, q, J=8.0Hz, CH_2); MS (ES^+) m/e 352 $[MH]^+$.

d) 3-Carboxamidoxime-5-(2,2,2)-trifluoroethyloxy-1,2,3a,4,6-pentaza-cyclopenta[a]naphthalene

To the preceding product (2.5g, 7mmol) in formic acid (213ml) and water (36ml), was added hydroxylamine hydrochloride (0.987g, 14mmol) and the reagents heated at 110°C for 20h. On cooling, the solvent was evaporated in vacuo and the residue triturated with water, filtered and washed successively with water and diethyl ether to give the title-product (1.1g, 50%), ^{1}H NMR (250MHz, d^6-DMSO) δ 12.51

and δ 12.30 (1H, 2 x s, C-H *E* and *Z*), 9.18 (1H, dd, J=4.5Hz and 1.4Hz, Ar-H), 8.93 (1H, dd, J=8.2Hz and 1.6Hz, Ar-H), 8.60 and 8.14 (1H, s, OH *E* and *Z*), 8.10 (1H, m, Ar-H), 5.29 (2H, q, J=8.8Hz, CH_2); MS (ES^+) m/e 313 $[MH]^+$.

e) 3-Carboxamidochloroxime-5-(2,2,2)-trifluoroethyloxy-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

To the preceding product (1.1g, 35mmol) in N,N-dimethylformamide (60ml) was added N-chlorosucciminide (0.471g, 35mmol) and the mixture heated briefly until the reagents were in solution. The mixture was allowed to cool, and poured into ice/water (100ml). The precipitate was filtered off, washed with water and ethanol and dried to give the title-compound (0.696g, 57%), ^1H NMR (250MHz, d^6-DMSO) δ 13.33 (1H, s, OH), 9.22 (1H, dd, J=4.5Hz and 1.5Hz, Ar-H), 8.98 (1H, dd, J=8.2Hz and 1.5 Hz, Ar-H), δ 8.11 (1H, m, Ar-H), 5.19 (2H, q, J=8.7Hz, CH_2).

f) 3-(5-Ethoxyisoxazol-3-yl)-5-(2,2,2-trifluoroethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

To the preceding product (692mg, 2mmol) in dichloromethane at room temperature under nitrogen was added ethoxyacetylene (40% solution in hexanes, 1.05g, 6mmol). A solution of triethylamine (0.28ml, 2mmol) in dichloromethane (30ml) was then added dropwise over 1h. The mixture was stirred for 1h, the solvent evaporated and the residue triturated with water and filtered. The solid was washed with water, hexane, and diethyl ether. Flash chromatography on silica gel, eluting with 2% → 4% methanol/dichloxomethane (gradient elution), gave the

title-compound (580mg, 76%), ^{1}H NMR (250MHz, $CDCl_3$) δ 9.22 (1H, dd, J=4.6Hz and 1.7Hz, Ar-H(9.02 (1H, dd, J=8.2Hz and 1.7Hz, Ar-H), 7.94 (1H, m, Ar-H), 6.06 (1H, s, Ar-H), 5.09 (2H, q, J=8.0Hz, CH_2), 4.41 (2H, q, J=7.1Hz, CH_2), 1.55 (3H, t, J=7.1Hz, CH_3).

g) 3-(5-Ethoxy-isoxazol-3-yl)-5-(1-methyl-1,2,4-triazol-3-ylmethyloxy)-1,2,3a,4,6-pentaaza-cyclopenta[a]naphthalene

The title-compound was prepared from the preceding product (145mg, 0.38mmol) and 1-methyl 1,2,4-triazole-3-methanol (prepared using the conditions of Itoh and Okongi, EP-A-421210) (47mg, 0.42mmol) following the procedure described in example 4 part b, ^{1}H NMR (360MHz, $CDCl_3$) δ 9.15 (1H, dd, J=4.5Hz and 1.7Hz, Ar-H), 8.99 (1H, dd, J=8.0Hz and 1.7Hz, Ar-H), 8.04 (1H, s, Ar-H) 7.87 (1H, m, Ar-H), 6.25 (1H, s, Ar-H), 5.79 (2H, s, CH_2), 4.43 (2H, q, J=7.1Hz, CH_2), 3.94 (3H, s, CH_3), 1.54 (2H, t, J=7.1Hz, CH_3); MS (ES^+) m/e 394 $[MH]^+$; Anal. Found. C, 51.34; H, 3.62; N, 31.91. $C_{17}H_{15}N_9O_2$. $0.1H_2O$ requires C, 51.67; H, 3.88; N, 31.90%.

Amyloid beta production inhibitors which can be used in the present invention are disclosed in WO-A-9828268, EP-A-0778266, WO-A-9838177, WO-A-9822494, WO-A-9822493, WO-A-9822441, WO-A-9822433, WO-A-9822430, WO-A-9825930, WO-A-9838156, US-A-5814646, WO-A-9620725, WO-A-9620949, US-A-5804560, GB-A-2309167 and WO-A-9855454.

Particularly favoured are compounds disclosed in WO-A-9822494, WO-A-9838177, EP-A-0778266 and W0-A-9828268.

Amyloid beta production inhibitors may be identified by any one of a number of known assays such as those disclosed in the above patent

literature. In particular the Cellular Screen given in Example Bio-1 of WO-A-9838177 may be used.

The present invention also provides a pharmaceutical composition comprising an amyloid β production inhibitor, an inverse agonist of the $GABA_A$ α_5 receptor subtype and a pharmaceutically acceptable carrier.

There is also provided a kit of parts comprising a first pharmaceutical composition comprising an amyloid β production inhibitor and a first pharmaceutically acceptable carrier and a second pharmaceutical composition comprising an inverse agonist of the $GABA_A$ α_5 receptor subtype and a second pharmaceutically acceptable carier for simultaneous, sequential or separate administration.

There is further provided a combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α_5 receptor subtype for use in a method of treatment of the human body, particularly for the treatment of a neurodegenerative disorder with associated cognitive deficit such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising from a normal process such as aging or of an abnormal process such as injury. The combination is particularly beneficial in the treatment of Alzheimer's Disease.

There is also provided the use of a combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α_5 receptor subtype in the manufacture of a medicament for the treatment of a neurodegenerative disorder such as Alzheimer's Disease or Parkinson's disease, or of a cognitive deficit arising from a normal process such as aging or of an abnormal process such as injury. The treatment of Alzheimer's Disease is particularly preferred.

There is also disclosed a method of treatment of a subject suffering from a neurodegenerative disorder, such as Alzheimer's Disease or

Parkinson's disease, or a cognitive deficit arising from a normal process such as aging or an abnormal process such as injury, which comprises administering to that subject a therapeutically effective amount of a combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α_5 receptor subtype. The treatment of Alzheimer's Disease is particularly preferred.

The pharmaceutical compositions of the present invention are preferably in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of each active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of each active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of

prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

For the treatment of a neurodegenerative condition, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day of each active ingredient. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, dosage outside these limits may be used.

The synergistic effect of the combination of the present invention can be shown, for example, by comparing the combined dosage of the combination with dosages of the same amount of each of the active ingredients separately on subjects using the Mini-Mental State Examination (MMSE) as described

in Folstein and Folstein J. Psychiat. Res., 1975, 12, 189-198 or a variant thereof as discussed in Tombaugh and McIntyre, JAGS, 1992, 40, 922.

These formulations may be prepared with separate active ingredients or with a combination of active ingredients in one composition. In such combined preparations, the ratio of the $GABA_A$ α5 inverse agonist and the amyloid β production inhibitor will depend upon the choice of active ingredients.

FORMULATION EXAMPLE 1 Tablets containing 50-300mg of $GABA_A$ α5 inverse agonist and 20mg of amyloid β production inhibitor

	Amount mg		
$GABA_A$ α5 inverse agonist	50.0	100.0	300.0
Amyloid β production inhibitor	20.0	20.0	20.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	169.5	119.5	119.5
Magnesium Stearate	0.5	0.5	0.5

The active ingredients cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 50mg, 100mg and 300mg of the $GABA_A$ α5 inverse agonist per tablet.

FORMULATION EXAMPLE 2 Parenteral injection

	Amount
Active Ingredients	10 to 300mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for injection	to 10ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The active ingredients are dissolved or suspended in the solution and made up to volume.

CLAIMS

1. A combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α5 receptor subtype for separate, simultaneous or simultaneous administration.

2. A kit of parts comprising a first pharmaceutical composition comprising an amyloid β production inhibitor and a first pharmaceutically acceptable carrier and a second pharmaceutical composition comprising an inverse agonist of the $GABA_A$ α5 subtype and a second pharmaceutically acceptable carrier for simultaneous, separate or sequential administration.

3. A combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α5 receptor subtype for use in a method of treatment of the human or animal body.

4. Use of a combination of an amyloid β production inhibitor and an inverse agonist of the $GABA_A$ α5 receptor subtype for the manufacture of a medicament for the treatment of a neurodegenerative disorder.

5. Use according to claim 4 wherein the neurodegenerative disorder is Alzheimer's Disease.

Application No: GB 0011430.6
Claims searched: 1-5
Examiner: Stephen Quick
Date of search: 29 November 2000

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.R):

Int Cl (Ed.7):

Other: Online: CAS ONLINE, EMBASE, EPODOC, JAPIO, MEDLINE, WPI

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Y	EP 0778266 A1	(BRISTOL-MYERS SQUIBB), see especially pages 2 (lines 3-7, 22-35 & 51-53), 3 (line 1ff) & 4 (lines 25-29); acknowledged in this application	1-5
Y	WO 98/50385 A1	(MERCK, SHARP & DOHME), see especially pages 1 (lines 4-9), 2 (lines 24-27) & 3 (lines 7-11 & 22ff) acknowledged in this application	1-5
Y	WO 98/38177 A1	(ATHENA NEUROSCIENCES & ELI LILLY), see especially pages 1 (lines 4-6), 4 (lines 17-31), 5 (lines 1-12, 15-20 & 21ff), 43 (lines 24-36) & 44 (lines 1-3); acknowledged in this application	1-5
Y	WO 98/18792 A1	(MERCK, SHARP & DOHME), see especially pages 3 (lines 12-17) & 24 (lines 22-26 & 27ff); acknowledged in this application	1-5
Y	WO 98/04560 A1	(MERCK, SHARP & DOHME), see especially pages 1 (lines 4-8) & 3 (lines 7-11 & 21ff); acknowledged in this application	1-5

X Document indicating lack of novelty or inventive step
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& Member of the same patent family
A Document indicating technological background and/or state of the art.
P Document published on or after the declared priority date but before the filing date of this invention.
E Patent document published on or after, but with priority date earlier than, the filing date of this application.

Application No: GB 0011430.6
Claims searched: 1-5

Examiner: Stephen Quick
Date of search: 29 November 2000

Category	Identity of document and relevant passage		Relevant to claims
Y	WO 96/25948 A1	(MERCK, SHARP & DOHME), see especially pages 1 (lines 6-14 & 21-24) & 2 (lines 8-22); acknowledged in this application	1-5

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Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
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